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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/120,044	07/21/98	MINETTI	C 1758-4036US2

HM12/0410

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EXAMINER	
DEVI,S	
ART UNIT	PAPER NUMBER
1645	28

DATE MAILED:
04/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/120,044	Minetti et al.
Examiner	**Group Art Unit**
S. Devi, Ph.D.	1645

☒ Responsive to communication(s) filed on *12/21/00.*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15, 22-26, and 31-34* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7, 22-26, and 31-34* is/are rejected.

☒ Claim(s) *3 and 8* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

1) The request filed on 21/12/2000 (paper no. 26) for a Continued Prosecution Application (C.P.A) under 37 C.F.R 1.53(d) based on parent Application, SN 09/120,044, is acceptable and a C.P.A has been established. An action on the C.P.A follows.

Applicants' Amendments

2) Acknowledgment is made of Applicants' preliminary amendment filed 12/21/2000 (paper no. 27) and the amendment filed 10/19/2000 (paper no. 21), which amendments have been entered.

Status of Claims

3) Claims 16-21 and 27-30 have been canceled via the amendment filed 12/21/2000.

Claims 1 and 2 have been amended via the amendment filed 12/21/2000.

Claims 1-15, 22-26 and 31-34 are pending.

Claims 1-15, 22-26 and 31-34 are under examination. An Action on the Merits for these claims is issued.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Drawings

6) The informal drawings filed in this application are accepted for examination purposes only. Formal drawings will be required when the application is allowed.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

7) Claims 1-7, 22-26 and 31-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

Applicants regard as the invention.

(a) Claims 1 and 2 are vague and indefinite in the recitation "refoldable", because it is unclear what is encompassed in this limitation. First, the recitation "refoldable" merely describes the potential capability of the modified pneumolysin to refold, but fails to positively recite that the modified pneumolysin in fact is refolded.

(b) Claim 1 is vague and indefinite in the recitation "similar" molecular weight (see part c), because "similar" is a relative term and it is unclear what degree of similarity in molecular weight is encompassed in this recitation.

(c) Claim 4 is confusing and/or redundant in the recitation "the amino acid sequence Formula I SEQ ID NO: 3" in line 3. The recitation of "Formula I" in line 3 is unnecessary. It is suggested that Applicants replace the former recitation with --the amino acid sequence of SEQ ID NO: 3--. It is further suggested that Applicants replace the recitation "said Formula I" with --said amino acid sequence-- in line 6.

(d) Claims 3-7, 22-26 and 31-34, which depend directly or indirectly from claim 1 or claim 2, are also rejected under 35 U.S.C § 112, second paragraph, as being indefinite, because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

8) Claims 1-7, 22-26 and 31-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(a) Independent claims 1 and 2, as amended, currently encompass a modified "refoldable" pneumolysin polypeptide having attenuated hemolytic activity and comprising an amino acid sequence of type 14 pneumolysin wherein at least one amino acid in the region comprising amino acid residues 1 to 257 of SEQ ID NO: 3 is substituted, "with the proviso that the substitution is not solely a substitution of isoleucine for threonine at position 172". However, there appears to be no descriptive or evidentiary support in the instant specification for this added limitation. Applicants point to page 5, line 28 through page 6, line 3 and Table 5A of the disclosure as support for the new limitation. Applicants state that this part of the specification

indicates "that threonine is the native amino acid at position 172". However, Table 5A does not even mention about a mutant pneumolysin bearing the threonine-to-isoleucine substitution at position 172, let alone a mutant, refoldable or non-refoldable and attenuated or hemolytic, having any additional mutation(s) in addition to the one at position 172. Secondly, the specification at page 5, line 28 through page 6, line 3, is not Applicants' invention, rather is a part of the 'Background of the Invention'. It is important to note that, via the sentences bridging pages 5 and 6 of the instant specification, Applicants concluded that the pneumolysin mutant disclosed by Lock *et al.* (*Microb. Pathog.* 21: 71-83, 1996 - Applicants' IDS) having threonine to isoleucine substitution at position 172 and reduced hemolytic activity "is incorrectly folded". However, now, Applicants point to the same part of the specification as supporting the new limitation in claims 1 and 2, i.e., "with the proviso that the substitution is not solely a substitution of isoleucine for threonine at position 172". A prior art mutant pneumolysin viewed by Applicants in the 'Background of the Invention' as "incorrectly folded" does not and cannot provide descriptive support for the new limitation now added to claims 1 and 2, which are drawn to a "refoldable" modified pneumolysin. What Applicants are trying to exclude from the scope of the claims using the proviso language is not disclosed. Most importantly, the mutant pneumolysin of Lock *et al.* mentioned on pages 5 and 6 of the specification is **not** of type 14 pneumococcus and therefore, cannot provide support for the claimed product. Therefore, the above-identified new limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation, or to remove the new matter from the claims.

(b) The recitation of the amino acid position "225" in claim 33 is new matter. There is no descriptive support within the instant specification for a modified pneumolysin polypeptide comprising the SEQ ID NO: 3 of type 14 pneumococcus having a substitution at position 225.

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the limitation, or to remove the new matter from the claim.

9) Claims 1-7, 22-26 and 31-34 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, claims 1-7, 22-26 and 31-34 encompass a modified refoldable pneumolysin polypeptide having attenuated hemolytic activity and comprising an amino acid sequence of type 14 pneumolysin wherein at least one amino acid in the region comprising amino acid residues 1 to 257 of SEQ ID NO: 3 is substituted, "with the proviso that the substitution is not solely a substitution of isoleucine for threonine at position 172". The basic requirement of the claimed modified, attenuated, refoldable type 14 pneumolysin double mutant, for example, is that it should have at least a substitution "of isoleucine for threonine at position 172" of the pneumolysin sequence **and** at least one amino acid substitution in the region comprising amino acid residues 1 to 257 of SEQ ID NO: 3. However, from Table 5A, it is apparent that neither a refoldable and attenuated mutant pneumolysin having only the substitution of isoleucine for threonine at position 172, nor a mutant having, in addition to the isoleucine for threonine substitution at position 172, an additional substitution(s) or mutation(s) in the region comprising amino acid residues 1 to 257 of SEQ ID NO: 3, is enabled. There appears to be no evidence within the instant specification enabling a double or triple or quadruple pneumolysin mutant comprising the threonine-to-isoleucine substitution at position 172 and any other mutation in the region comprising amino acid residues 1 to 257 of SEQ ID NO: 3, with or without having refoldable and attenuated hemolytic properties. By the proviso recitation that "the substitution is

not solely a substitution of isoleucine for threonine at position 172", it is claimed that the mutant has additional mutations or substitutions at any other position in the region of 1 through 257 of SEQ ID NO: 3 in addition to the substitution of isoleucine for threonine at position 172. However, the basic requirement itself for the claimed product is non-enabled. What is claimed is not enabled. The recited functions of refoldability and attenuated hemolytic activity of the claimed product cannot be attributed to a modification(s) or substitution(s) that has not been attained by the Applicants. Clearly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific and adequate evidence and/or guidance, lack of working examples enabling the claimed product, quantity of experimentation necessary, and the breadth of claims.

10) Claims 1-7, 22-26 and 31-34 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a refolded, modified, hemolytically attenuated, pneumolysin polypeptide obtained by mutating the nucleic acid molecule encoding type 14 wild-type pneumolysin having SEQ ID NO: 3 in a region comprising 17 and 18, 33, 41 through 46, 61 through 66, 83, 101, 102, 127, 128, 148, 172, 189, 195, 239, 255 and 257, does not reasonably provide enablement for a modified and attenuated refoldable type 14 pneumolysin having one or more amino acid substitutions in the region of SEQ ID NO: 3 comprising amino acid residues 1 through 16, 19 through 32, 34 through 41, 42 through 44, 47 through 60, 67 through 82, 84 through 100, 103 through 126, 129 through 147, 149 through 171, 173 through 188, 190 through 194, 196 through 238 and 240 through 254, as claimed broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;

- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention includes modifying or attenuating type 14 wild-type pneumolysin polypeptide by random mutation of the nucleic acid molecule, which encodes the wild type pneumolysin. The breadth of the claims encompasses any refoldable, modified, hemolytically attenuated, pneumolysin polypeptide obtained by mutation of the nucleic acid molecule encoding type 14 wild type pneumolysin at **any** random position or positions in the region comprising amino acid residues 1 to 257. However, a review of instant disclosure suggests that the entire scope of the claims is not enabled.

It has been established in the art that attenuation of the hemolytic activity of a wild-type pneumolysin by any random mutation is an unpredictable event. For instance, Feldman *et al. (Am. J. Respir. Cell Mol. Biol.* 5: 416-423, 1991, already of record) show that, while a Trp 433 > Phe modification results in a modified pneumolysin having a lowered haemolytic activity, a Tyr 384 > Phe modification results in a modified pneumolysin that had normal hemolytic activity (see page 417). The state of the art clearly suggests that a mutation at any random position does not always result in a modified pneumolysin polypeptide having an attenuated hemolytic activity. Mitchell *et al.* (*Mol. Microbiol.* 5: 1883-1888, 1991, already of record) show that individual modifications of Trp 379 and Trp 397 to Phe, or of residues Tyr 384 and Asp 385 to Phe and Asn respectively, did not alter the cytolytic activities of resultant modified pneumolysins (see page 1885, left column). The state of the art at the time Applicants filed one of their provisional applications, SN 60/073,456, shows that an Asp 385 >Asn mutation in the pneumolysin gene resulted in a modified pneumolysin that retained 100% hemolytic activity of wild-type pneumolysin (see Table 1 of Alexander *et al. Microb. Pathogen.* 24: 167-174, March 1998, already of record). The specification acknowledges on page 26, lines 6-9, that several positions that fall in the range of amino acid residues 1-57 "are not associated with decreases in hemolytic activity". In the paragraph bridging pages 25 and 26 and on page 26, the specification states that the amino acid substitutions at position 17, 18, 33, 41, 45, 46, 63, 66, 83, 101, 102, 127, 128, 172, 189, 239,

255 and 257 of the pneumolysin alone "do not reduce hemolytic activity" and that these sites are not associated with decreases in hemolytic activity. See Table 3. It appears that a single amino acid substitution at these identified positions would not yield an attenuated pneumolysin, yet these mutants are currently encompassed in the scope of the broad claims.

Similarly, the specification discloses that even with a substitution at a single amino acid position (let alone combination of substitutions), the refoldability of the resultant single mutant polypeptide is not predictable. For instance, the specification discloses that a single mutation at position 243 of the wild-type pneumolysin, or a combination of substitutions that includes position 243, resulted in insoluble inclusion bodies, and attempted refolding of the mutant yielded aggregate species (see pages 57 and 58, and Table 5B). Obviously, such an insoluble and non-refoldable or non-functional pneumolysin would lack the structural, functional and immunogenic and/or biological integrity, and therefore, is not an ideal protein carrier for preparation of polysaccharide conjugates of claims 22-26.

As recited currently in a broad sense, a myriad of random mutations and combinations thereof of the wild-type pneumolysin nucleic acid is encompassed in the scope of the claims. However, the specification states that multiple mutations are unpredictable and may act synergistically to abolish activity. In view of the recognized unpredictability of obtaining an attenuated pneumolysin by any random mutation(s), Applicants' own evidence showing that refoldable and hemolysis-attenuating properties of even a single mutant of pneumolysin in the recited region is an unpredictable event, the quantity of experimentation necessary and the breadth of the claims, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the full scope of the invention as claimed. The breadth of instant claims is not commensurate in scope with the enabling disclosure and/or evidence and clearly, one skilled in the art cannot make and use the invention commensurate in scope with the claims without undue experimentation.

Objection(s)

11) Claims 3, 8 and 33 are objected to for reasons given below:

(a) Claims 3 and 8 lack a period at the end.

(b) In claim 33, for clarity, it is suggested that Applicants replace the recitations of ";"

in line 5 of the claim with --,--.

Remarks

12) Independent claims 7 and 9-15 stand allowed. Claim 8 stands objected to. Claims 1-7, 22-26 and 31-34 stand rejected.

13) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week.

14) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.45 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD/:
S. Devi, Ph.D.
Patent Examiner
April 2001